Title

Modified Antiretroviral Treatment Access Study (MARTAS): A Randomized Controlled Trial of the Efficacy of a Linkage-to-Care Intervention Among HIV-Positive Patients in Ukraine

Journal

AIDS and Behavior, 24(11)

ISSN

1090-7165

Authors

Neduzhko, Oleksandr
Postnov, Oleksandr
Sereda, Yuliia
et al.

Publication Date

2020-11-01

DOI

10.1007/s10461-020-02873-7

Peer reviewed

HHS Public Access

Author manuscript

AIDS Behav. Author manuscript; available in PMC 2020 November 01.

Published in final edited form as:

AIDS Behav. 2020 November ; 24(11): 3142–3154. doi:10.1007/s10461-020-02873-7.

Modified Antiretroviral Treatment Access Study (MARTAS): A Randomized Controlled Trial of the Efficacy of a Linkage-to-Care Intervention Among HIV-Positive Patients in Ukraine

Oleksandr Neduzhko[1], **Oleksandr Postnov**[1], **Yuliia Sereda**[1], **Roksolana Kulchynska**[2], **Trista Bingham**[3], **Janet J. Myers**[4], **Timothy Flanigan**[5], **Tetiana Kiriazova**[1]

[1]Ukrainian Institute on Public Health Policy, 5 Mala Zhytomyrska str., Office 61A, Kiev 01001, Ukraine

[2]Division of Global HIV and TB, U.S. Centers for Disease Control and Prevention, Kiev, Ukraine

[3]Division of Global HIV and TB, U.S. Centers for Disease Control and Prevention, Atlanta, USA

[4]Prevention Research Center, University of California, San Francisco, USA

[5]Alpert Medical School, Brown University, Providence, USA

Abstract

Between October 2015 and March 2018, we conducted the Modified Antiretroviral Treatment Access Study (MARTAS), a nurse-delivered case management intervention to improve linkage-to-care for persons recently tested HIV positive. Adult participants from nine urban clinics in three regions of Ukraine were randomized to either MARTAS or standard of care (SOC) using individual, parallel, two-arm design. The main study outcome was linkage-to-care (defined as registration at an HIV clinic) within a 3-month period from enrollment in the study. Intention-to-treat analysis of MARTAS (n = 135) versus SOC (n = 139) showed intervention efficacy in linkage to HIV care (84.4% vs. 33.8%; adjusted RR 2.45; 95% CI 1.72, 3.47; $p < 0.001$). MARTAS is recommended for implementation in Ukraine and may be helpful in other countries with similar gaps in linkage-to-care. Clinicaltrials.gov registration number: NCT02338024.

Keywords

HIV care; Nurse case management; Linkage-to-care; Randomized controlled trial

Oleksandr Neduzhko, neduzhko@uiphp.org.ua.

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol and instruments were approved by the institutional human subjects review board at the UIPHP under FWA00015634. The protocol was also reviewed in accordance with the U.S. Centers for Disease Control and Prevention (CDC) human research protection procedures and determined to be research, but CDC investigators did not interact with human subjects or have access to identifiable data or specimens for research purposes. The study was registered in clinicaltrials.gov NCT02338024.

Informed Consent Written informed consent was obtained from all individual participants included in the study.

Research Involving Human Participants and/or Animals This article does not contain any studies with animals performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Introduction

Global estimates show decreases in the HIV epidemic from 2.7 million new HIV infections in 2010 to 1.8 million in 2017 and a decrease from 1.8 million AIDS-related deaths in 2010 to 940,000 in 2017 [1, 2]. In contrast, the number of new HIV infections in Eastern Europe and Central Asia (EECA) has grown by 30%, from 74,000 to 100,000 new HIV cases between 2010 and 2017, and only 36% of people living with HIV (PLHIV) in EECA received antiretroviral therapy (ART) in 2017 [2]. In Ukraine, most people living with HIV (PLHIV) achieve linkage-to-care when they have advanced HIV disease and low $CD4^+$ T-lymphocyte count (below 350 cells/μl) [3], Among the estimated 244,000 PLHIV in Ukraine in 2017, only 141,371 (57.9%) were linked to HIV care; of these, 98,237 (69.5%, and 40.3% of all PLHIV) were receiving ART [3].

In Ukraine, Dnipropetrovsk, Mykolaiv and Odesa are among the regions most burdened by the HIV epidemic, with HIV prevalence ranging from 769.6 to 885.4 per 100,000 population compared to the national average of 333.3 per 100,000 [3]. The 2017, the Ukrainian Integrated Biological and Behavioral Surveys found an overall HIV prevalence of 22.6% among people who inject drugs (PWIDs) nationwide, and 29.9%, 28.7% and 18.7%, respectively, among PWIDs in Dnipropetrovsk, Mykolaiv and Odesa regions [3].

Studies have revealed multiple barriers to linkage and retention in HIV care, including patient-related factors (younger age, good health condition, HIV status denial, lack of insurance, perceived lack of need for medication, other life priorities, mental illness, substance use, low socio-economic status, internalized stigma) and system-level factors (long waiting times at HIV clinics, limited access to ART, HIV-related discrimination) [4-8]. Lower educational level, good health status, and injection drug use are the barriers to HIV care particularly relevant to Ukraine [9, 10].

Country-specific treatment guidelines may also inhibit access to HIV care [11]. For instance, a person who presents for an initial medical examination during registration in HIV care, is a subject to 16 laboratory tests and instrumental examinations (such as chest X-ray and abdominal ultrasound) including mandatory HIV retesting [12]. The presence of comorbidities and opportunistic infections requires additional medical examinations leading to further delays. This complex process of linkage-to-care creates a challenging system-level barrier [10].

Timely linkage-to-care and early ART initiation substantially improves treatment outcomes and reduces HIV transmission [13, 14]. These findings underscore the need to implement effective strategies to link and retain patients in HIV care [7, 15-17]. While several interventions for improving linkage and retention in care have been studied [15, 18-20], the ARTAS-I (Antiretroviral Treatment and Access Study) trial is the only randomized controlled trial (RCT) that examined an HIV case management intervention to improve linkage-to-care [7, 21]. The ARTAS-II implementation study evaluated the same intervention in health departments and community-based organizations [5]. Both studies found similar rates of linkage to HIV medical care within 6 months among the intervention

participants (ARTAS-I, 78%; ARTAS- II, 79%) [5, 21]. Inspired by this model, in this paper, we report the results of a multi-site, two-arm RCT design evaluating the efficacy of an individual-level, nurse-delivered case management intervention, Modified ARTAS (MARTAS), to link and retain PLHIV in HIV care in Ukraine.

Methods

Study Design and Settings

We conducted the MARTAS individual, parallel, two-arm, 1:1 RCT during October 2015–March 2018. The study participants were recruited between October 2015 and December 2016 at 9 clinics located in Dnipropetrovsk region (Dnipropetrovsk Regional Narcological Dispensary; Dnipropetrovsk Regional Dermatovenereologic Dispensary; Kryvyi Rih Infectious Disease Clinic No. 1), Mykolaiv region (Mykolaiv Regional Narcological Dispensary; Mykolaiv Regional Dermatovenereologic Dispensary; Mykolaiv Regional Infectious Disease Clinic), and Odesa region (Odesa Regional Dermatovenereologic Dispensary; Odesa Infectious Disease Clinic; Odesa Regional Center of Mental Health). These three types of clinical sites (treating addiction, sexually transmitted infections [STIs], and infectious diseases [IDs]) were located in the regions with the highest HIV prevalence in Ukraine, but were not co-located with HIV care facilities. Participants assigned to the standard of care (SOC) arm and the MARTAS arm received referrals to the local AIDS Centers (Dnipropetrovsk Regional AIDS Center, Kryvyi Rih AIDS Center, Mykolaiv Regional Center for Palliative Care and Integrated Services (former Mykolaiv AIDS Center), and Odesa Regional AIDS Center) or their departments (“Trust” offices) located in each study region. Investigators affiliated with The Ukrainian Institute on Public Health Policy (UIPHP) were responsible for all aspects of study design, management, and analysis.

Study Population and Recruitment

Individuals were initially eligible for this study if they were patients of the nine study clinics, tested HIV-positive within the past 12 months, were 18 years or older, were fluent in Russian or Ukrainian, and were able to read, understand and sign an informed consent form. After the first 6 months of recruitment, the eligibility criterion of being tested HIV-positive within the past 12 months was expanded to all HIV-positive individuals attending the study sites who had never been linked to HIV care. Exclusion criteria were: previously linked to HIV care; cognitive impairment; participation in a similar linkage-to-care intervention; plans to move out of the study region before the end of study follow-up; and currently being under criminal investigation. During post-test HIV counselling or at a regular clinical visit, clinic physicians provided potential participants with information about the study and referred interested participants to the study recruiters located in a private room in the same clinic for the screening, consent, baseline assessment and randomization.

Study Procedures

All participants completed an interviewer-assisted baseline interview and were scheduled for 3- and 6-month follow-up interviews. Participants’ data were collected using paper-based structured questionnaires (baseline, 3- and 6-month follow-up) and medical chart review forms at the AIDS Centers. Medical information was extracted into study forms by a study

team member hired among the personnel of participating AIDS Centers to ensure legal access to medical and HIV case reporting information. Participants received the equivalent of $20 USD as compensation for their time and transportation costs. Compensation for participation in the MARTAS intervention was not provided.

An intervention manual was adapted for use in this context by study investigators; MARTAS case managers, medical chart reviewers, supervisors and recruiters/interviewers received a 5-day training. Two case managers were trained per each participating recruitment site (clinic) to address potential staff turnover. The research team conducted weekly conference calls and monthly monitoring visits to study sites during the first 3 months and then every 3 months during the data collection period.

Randomization

Random allocation was performed by the study statistician using the "*runif* function of R Studio software (Version 0.98.1091—©2009–2014 RStudio, Inc.). Participants were enrolled and assigned to the MARTAS intervention or the SOC arm by recruiters/interviewers in a 1:1 fashion using a block size of four from sealed envelopes. Recruiters were not aware of the size of the blocks, and envelopes were not transparent. Randomization occurred after participants completed their baseline interview.

Intervention (MARTAS) and Control (SOC) Arms

Participants assigned to the SOC arm received oral referrals to a network of government AIDS Centers or their departments ("Trust" offices) located in each study region; these Centers/departments are the only places to complete linkage (registration) to HIV care and ART initiation. SOC did not include case management.

Participants randomized to the intervention arm were introduced to the Linkage Coordinator (LC)—a trained nurse who provided the MARTAS (Modified ARTAS) intervention. ARTAS is an individual-level, multi-session case management linkage-to-care intervention [21], based on the Strengths-based Case Management (SBCM) model [22, 23], which borrows from theories of empowerment and self-efficacy [24, 25]. SBCM encourages a client to identify and use personal strengths, set personal goals, and establish an effective relationship with the LC. The modifications to the original ARTAS intervention were made based on the results of the formative research [26] and pilot feasibility and acceptability study [27] (Table 1). The MARTAS case management intervention consists of six sessions with the LC (three in person and three by phone) and text messaging reminders during a 3-month period. Objectives include linkage to HIV care, addressing depression, issues pertaining to stigma as a barrier to care, HIV status disclosure, and substance use disorder issues. At each participating healthcare facility, LCs were hired from existing nurse staff.

Contact with the intervention participants was maintained according to the participants' preferred method. At the conclusion of the first individual session, the LC gave the participant an appointment card with the time and location of the second individual session and provided reminder calls/texts if needed. The individual sessions were held in private rooms at the participating clinics. Clients who missed their appointments were contacted

immediately to schedule a new session. If needed, LCs would accompany the patient to the AIDS Center or Trust office. LCs might contact HIV physicians and community managers of non-governmental organizations based at the AIDS Centers and Trust offices, to help participants with linkage-to-care. All intervention activities were required to be completed within 3 months after randomization so that no further intervention-related contacts between the LC and the participant were supposed to take place.

Outcome Definition Study Endpoints

The primary outcome for the intervention was linkage (registration) to HIV care (yes/no) within the 3-month period after study enrollment—both self-reported and confirmed by the medical record. The 3-month period was selected based on the international recommendations [28] at the time and from studies with similar outcomes [11]. We reviewed medical records to verify the participants' self-reported linkage to HIV care. All randomized and eligible participants were included in the main analysis to evaluate the effects of the MARTAS intervention on linkage-to-care at the AIDS Center within 3 months from the date of enrollment in the study (date of informed consent).

Data on secondary study outcomes were obtained from the medical records: (1) linkage, defined as first HIV clinical visit within 3 months after study enrollment (yes/no); (2) retention, defined as at least one additional HIV clinical visit within 6 months after linkage to HIV care (yes/no); (3) time to linkage (days from baseline) to HIV care for drug users and non-drug users (days). The outcome "first HIV clinical visit within 3 months" was substituted for ART initiation due to recurrent HIV test kit stock-outs in 2016 delaying HIV retesting for verification, which was required for ART initiation.

Predictors

Predictor variables included facility type (STI, addiction, and ID clinics) and socio-demographic and behavioral patient characteristics (Table 2). Frequency of depressive symptoms during the past week was measured using the Center for Epidemiologic Studies Depression Scale (CES-D) [29, 30] with a cutoff of 16 as a screening criterion [31]; risk of alcohol dependence was measured using Alcohol Use Disorders Identification Test (AUDIT) with four risk levels (zones) of alcohol dependence [32]; experience of HIV symptoms within the past 4 weeks using HIV symptoms index [33, 34]; HIV status disclosure; HIV knowledge [correct answers to all 10 questions adapted from Demographic and Health Surveys Model Questionnaire [35]]; time since HIV diagnosis to study entry (months). We also explored HIV clinical stage (I–II, III–IV), and HIV immunological stage [CD4 count (cells/μl)] [36] (for those linked to HIV care).

Statistical Analysis

Data on the primary and secondary outcomes were analyzed by intention-to-treat principles: all were analyzed in the randomization group to which they were originally assigned, including two participants who failed to keep any appointments with the LC. Descriptive analyses were performed to compare baseline characteristics between the study arms using Pearson's chi-square test with Yates's correction for categorical variables and Mann–Whitney U tests for continuous variables ($p < 0.05$ for statistical significance). Fisher's exact

test was used for categorical variables with expected counts below five. The effect of MARTAS on outcomes of interest was measured by log-binomial regressions. Crude and adjusted relative risks (RR) and 95% confidence intervals (CI) were calculated for the primary outcome. Wald test statistics were used for testing of associations (i.e., RR and adjusted RR not equal to 1.0). The purposeful selection of covariates from the list of study variables was used for multivariable regression analysis. In the iterative process of variable selection, covariates were excluded from the model if they had a p-value over 0.20 in binary log-binomial models and/or were not considered a priori as a potential confounder. Confounders were defined as a change in the MARTAS estimate greater or equal to 5%. Variables that were considered but were not included in the multivariable regression model were: type of site, age, relationship status, employment, average monthly income, AUDIT score, HIV symptoms index, HIV bothersome symptoms index, HIV status disclosure, HIV knowledge, and time since HIV positive testing to study entry. For variables with missing data, we conducted a complete-case analysis.

Additionally, we estimated differences in time of enrollment in HIV care between intervention and control arms for drug users and non-drug using participants using Kaplan–Meier curves and Log-rank test. The Kaplan–Meier survival function was transformed as one-survival to show cumulative probability of having the event (linkage-to-care). Drug users were defined as participants who reported any illicit drug use (injecting or/and non-injecting) except cannabis and opioid substitution therapy (OST) during last 30 days at baseline (N = 53); most of the drug-using participants were PWIDs (N = 49). Analysis was performed in SPSS 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) and R version 3.5.2 (The R Foundation for Statistical Computing).

Sample Size Assumptions

Our planned study sample included 276 participants (138 intervention and 138 control participants). We used the software package G*Power version 3.1.5 to estimate sample size based on the assumption of at least 20% absolute difference between the proportion of referred patients who were linked to HIV care within 3 months in the intervention group (70%) compared to the control group (50%).

Results

We assessed 280 patients for eligibility, 276 were eligible, consented and were randomized (Fig. 1); 137 and 139 participants were randomized to the intervention group and SOC, respectively. Two participants of the intervention arm were later excluded from the study because of not meeting eligibility criteria (one subject had a false positive HIV test result, and another subject initially concealed that he had been already linked to HIV care). The final number analyzed in the MARTAS intervention arm was 135.

One hundred and twenty-four (91.9%) intervention group participants and 124 (89.2%) control group participants completed the 3-month follow-up assessment. One hundred and twenty-one (89.6%) intervention group participants and 120 (86.3%) control group participants completed the 6-month follow-up assessment. The reasons for the loss to follow-up are shown in the Fig. 1. The overall follow-up rate was 241 of 274 (88.0%).

Twenty-two deaths, none related to the study, occurred over the course of the RCT. Most patients who died (n = 15; 68.2%) were recruited at in-patient departments of ID clinics with severe manifestations of HIV/AIDS.

Baseline Characteristics of Study Participants

In the study, we achieved balance in the distributions of most baseline characteristics as a result of the randomization between the intervention and SOC groups (Table 2). Almost half were recruited from STI clinics. The median age was 36 and ranged from 18 to 66 years. The majority were male (63.5%), married or cohabitating with regular partner (53.6%), with high school/vocational education (59.5%), employed full-time or part-time (75.8%), and had their own apartment/house (53.6%). Over half (53.3%) of SOC participants and 39.3% of MARTAS participants had a personal monthly income ≤ 2000 UAH (≤ $80 USD) ($\chi^2$ = 4.830, p = 0.028). Less than one quarter of all participants had a history of incarceration (24.5%); 19.3% had used drugs during past 30 days (injecting or/and non-injecting), excluding cannabis and OST. Similar proportions (12.7% vs. 20.1%, χ^2 = 2.241, p = 0.13) of MARTAS and SOC participants had alcohol dependence (AUDIT Zone IV (20–40), and 67.4% vs. 73.4% (χ^2 = 0.904, p = 0.34), correspondingly, were regular smokers.

Over half of participants in the intervention and control groups had depression symptoms (≥ 16 points CES-D) [56.3% in intervention group and 57.6% in the control group (χ^2 = 0.008, p = 0.93)]. Participants in both groups had almost the same median frequency of HIV symptoms (8.0 in the intervention arm vs. 7.0 in the SOC, Mann–Whitney U = 9228.5, p = 0.81) and the same HIV bothersome symptoms median frequency (2.0). One third of participants in each group did not disclose their HIV-positive status to anyone [34.1% of intervention and 33.1% of control participants, (χ^2 = 0.002, p = 0.97)]. Both MARTAS participants and control group participants had low levels of HIV knowledge at baseline: 11.1% of intervention group and 16.5% of control group gave correct answers to all ten questions about HIV transmission and prevention (χ^2 = 1.270, p = 0.26). The majority of participants, 97.8% in the intervention group and 95.7% in the control group, had tested HIV positive within 6 months prior to enrollment into the study (Fisher's Exact Test, p = 0.50).

Contacts with the Nurse Linkage Coordinator

The majority of the intervention group participants, 133 (98.5%) received at least one MARTAS session. On average, participants received 3.2 sessions (SD 1.0), including face-to-face—2.8 (SD 0.8) and phone sessions—0.3 (SD 0.5) sessions. The average duration of face-to-face sessions was 52.4 (SD 33.3) min; the average duration of phone sessions was 21.5 (SD 9.5) min. More than half of the MARTAS sessions (50.8%) were conducted at the study sites, and 36.2% at clinics other than study sites (including AIDS Centers and Trust offices). The average number of sessions during which clients received a strengths assessment was 1.4 (SD 0.7). On average, clients received 2.3 (SD 1.2) referrals to HIV services and 0.75 (SD 0.7) referrals to other services.

Multivariable Analysis of Linkage to HIV Care (Main Study Outcome)

The analysis of the main study outcome showed that the MARTAS intervention was associated with higher likelihood of linkage to HIV care (84.4% vs. 33.8%; crude RR 2.50;

95% CI 1.96, 3.19; $p < 0.001$; adjusted RR 2.45; 95% CI 1.72, 3.47; $p < 0.001$) (Table 3). Medical records (without confirmation by self-report) demonstrated slightly higher proportions of those linked to care in both study arms (MARTAS—87.4% vs. SOC—38.1%; crude RR 2.29; 95% CI 1.84, 2.86; $p < 0.001$; adjusted RR 2.25: 95% CI 1.61, 3.14, $p < 0.001$).

Most participants (52.2%) were linked to HIV care with advanced and severe HIV infection (III-IV clinical stages) (MARTAS—48.2% vs. SOC—61.7%; $\chi^2 = 1.906$, $p = 0.167$). Among 153 participants linked to HIV care and with available CD4 count data, 96 (62.7%) presented to care with advanced and severe immune suppression (CD4 count ≤ 349 cells/μl) (MARTAS—65.1% vs. SOC—57.4%; $\chi^2 = 0.520$, $p = 0.471$).

First HIV Clinical Visit Within 3 Months After Study Enrollment and Analysis of Retention in HIV Care (Secondary Study Outcomes)

According to the medical record data, a higher proportion of 135 MARTAS participants than 139 SOC participants made their first clinical visit (regardless of further registration) to an HIV clinic within 3 months after study enrollment (89.6% vs. 42.4%; crude RR 2.11, 95% CI 1.73, 2.58, $p < 0.001$). Among all study participants, 87 out of 135 (64.4%) MARTAS participants and 45 out of 139 (32.4%) control group participants were retained in care at 6 months after registration (crude RR 1.99; 1.52, 2.61; $p < 0.001$).

Time to Linkage to HIV Care

Log-rank test results showed significant difference between groups on time to linkage to HIV care (Log Rank = 72.6, $p < 0.001$) (Figs. 2, 3. and 4). The difference between MARTAS and SOC groups on time to linkage-to-care was statistically significant among both active drug users ("injecting or/and non-injecting drug use during last 30 days excluding cannabis and OST") (Log Rank = 43.3, $p < 0.001$) and participants who didn't report drug use in the past month (Log Rank = 40.2, $p < 0.001$).

Discussion

This study provides strong evidence of efficacy of an individual nurse-delivered case management intervention, MARTAS, in Ukraine. In this RCT conducted at nine urban clinics among 274 HIV-positive participants, almost all of whom (96.7%) were tested HIV-positive within past 6 months, the MARTAS intervention was associated with a doubling in linkage to HIV care within 3 months compared with the SOC group. To the best of our knowledge, the MARTAS study is the only RCT that has examined a nurse-delivered case management intervention to improve linkage and retention in HIV care in the EECA countries.

The results of multivariable analysis demonstrated that receiving the MARTAS intervention was associated with 2.45 times greater increase in linkage to HIV care within 3 months compared with the SOC arm. MARTAS was also associated with a twofold increase in retention in HIV care following initial linkage to HIV care. Based on the log-rank test results, the intervention also worked well for those participants who were active drug users. The effects we observed among active drug users in MARTAS was an improvement over

what was observed in the ARTAS or ARTAS II studies [5, 21]. For example, subgroup analysis of the ARTAS results showed that PLHIV who used crack cocaine or injected drugs recently and those who had symptoms of depression, were among four demographic, behavioral, and psychological subgroups in which ARTAS was not successful in linking recently diagnosed PLHIV to medical care [37]. Based on their findings, the authors concluded that the intervention might need to be tailored to the specific needs of such groups. Taking this into account and based on our formative research results [26], we made modifications to the ARTAS intervention, to address Ukraine-specific barriers to HIV care, such as drug use and depressive symptoms (Table 1). Accordingly, LCs discussed with the MARTAS participants their drug use problems and available drug treatment and sources of support. This may be the reason why MARTAS was successful among the subgroup of drug-using participants in Ukraine. In addition, this study was adjusted to the Ukrainian context by selection of MARTAS recruitment sites where key populations often receive medical care and by excluding patients participating in a similar linkage-to-care intervention.

The U.S. experience demonstrated that access to HIV surveillance databases was useful to locate HIV patients who were lost to care according to individual clinic medical records but in fact were in care at another HIV clinic [38, 39]. In our study, a staff member at each AIDS Center was authorized to review medical charts and confidential HIV surveillance data, and the information from all HIV facilities across the region was available. This approach was used to examine whether participants who were not interviewed at follow-up assessments were actually engaged in HIV care.

Although this study was designed as an RCT, it is important to note some potential limitations. First, our paper-based structured interview guide could have resulted in less accurate self-reported data on personal behaviors compared with Audio Computer-Assisted Self-Interview collected data [40, 41]. Second, the study was implemented in urban areas with high HIV prevalence and a concentration of key populations at the selected types of clinics, which may limit the generalizability of the findings to the areas with lower HIV prevalence or in other types of clinics.

One of the study strengths is that nurses who were already based at the study sites acted as the intervention linkage coordinators. This approach may ensure higher sustainability of the intervention at the clinics in Ukraine once funding for HIV services by international donors wanes. Future interventions designed to improve linkage to HIV care should assess more strategies to decrease the time between diagnosis and linkage-to-care for newly diagnosed HIV patients, improve long-term retention and durable viral load suppression as the ultimate outcomes of HIV treatment cascade.

Conclusions

Overall, we found that a nurse-delivered case management intervention (MARTAS) resulted in significantly improved linkage to HIV care and retention at 6 months among patients who had recently tested HIV-positive. This intervention could be implemented at health departments in Ukraine and in other EECA countries where the HIV epidemic is

concentrated among key populations, specifically PWID, who often seek medical care at similar types of specialized clinics.

Acknowledgements

We would like to thank Dr. Sherri L. Pals (CDC, Division of Global HIV and Tuberculosis) for advice and comments on statistical aspects. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies.

Funding This project has been supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through the U.S. CDC under the terms of Grant 3U01GH000752-02S1.

References

1. UNAIDS Data Tables. 2011 https://www.unaids.org/sites/default/files/media_asset/JC2225_UNAIDS_datatables_en_1.pdf. Accessed 27 Dec 2019.
2. UNAIDS data. 2018 https://www.unaids.org/sites/default/files/media_asset/unaids-data-2018_en.pdf. Accessed 19 Sept 2018.
3. Ukrainian Center for Public Health. 2018 HIV infection in Ukraine. Informational Bulletin No. 49. https://phc.org.ua/uploads/documents/c21991/40fc8f955d5286e602e5ce1e8fac0fe2.pdf. Accessed 19 Sept 2018.
4. Maulsby C, Sacamano P, Jain KM, et al. Barriers and facilitators to the implementation of a national HIV linkage, re-engagement, and retention in care program. AIDS Educ Prev. 2017;29(5):443–56. [PubMed: 29068718]
5. Craw JA, Gardner LI, Marks G, et al. Brief strengths-based case management promotes entry into HIV medical care: results of the antiretroviral treatment access study-II. J Acquir Immune Defic Syndr. 2008;47(5):597–606. [PubMed: 18285714]
6. Wohl AR, Dierst-Davies R, Victoroff A, et al. Implementation and operational research: the navigation program: an intervention to reengage lost patients at 7 HIV clinics in Los Angeles County, 2012–2014. J Acquir Immune Defic Syndr. 2016;71(2):e44–50. [PubMed: 26484741]
7. Giordano TP. Strategies for linkage to and engagement with care: focus on intervention. Top Antivir Med. 2018;26(2):62–5. [PubMed: 29906790]
8. Govindasamy D, Ford N, Kranzer K. Risk factors, barriers and facilitators for linkage to antiretroviral therapy care: a systematic review. AIDS. 2012;26(16):2059–67. [PubMed: 22781227]
9. Kiriazova TK, Postnov OV, Perehinets IB, Neduzhko OO. Association of injecting drug use and late enrolment in HIV medical care in Odessa Region. Ukraine HIV Med. 2013;14(Suppl 3):38–41. [PubMed: 24033902]
10. Neduzhko O, Postnov O, Perehinets I, et al. Factors associated with delayed enrollment in HIV medical care among HIV-positive individuals in Odessa Region, Ukraine. J Int Assoc Provid AIDS Care. 2017;16(2):168–73. [PubMed: 28034344]
11. Croxford S, Burns F, Copas A, et al. Factors associated with delayed linkage to care following HIV diagnosis in the WHO European Region. HIV Med. 2018;19(Suppl 1):40–6. [PubMed: 29488702]
12. Ministry of Health of Ukraine. (2010) About approving the clinical protocol of antiretroviral therapy of HIV infection in adults and adolescents. https://zakon.rada.gov.ua/rada/show/v0551282-10. Accessed 27 Sept 2018.
13. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. N Engl J Med. 2016;375(9):830–9. [PubMed: 27424812]
14. Ulett KB, Willig JH, Lin HY, et al. The therapeutic implications of timely linkage and early retention in HIV care. AIDS Patient Care STDS. 2009;23(1):41–9. [PubMed: 19055408]
15. Brennan A, Browne JP, Horgan M. A systematic review of health service interventions to improve linkage with or retention in HIV care. AIDS Care. 2014;26(7):804–12. [PubMed: 24354712]
16. Eaton EF, Saag MS, Mugavero M. Engagement in human immunodeficiency virus care: linkage, retention, and antiretroviral therapy adherence. Infect Dis Clin North Am. 2014;28(3):355–69. [PubMed: 25151561]

17. Govindasamy D, Meghij J, Kebede Negussi E, et al. Interventions to improve or facilitate linkage to or retention in pre-ART (HIV) care and initiation of ART in low- and middle-income settings–a systematic review. J Int AIDS Soc. 2014;17:19032. [PubMed: 25095831]
18. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. Ann Intern Med. 2012;156(11):817–33. [PubMed: 22393036]
19. Bradford JB, Coleman S, Cunningham W. HIV system navigation: an emerging model to improve HIV care access. AIDS Patient Care STDS. 2007;21(Suppl 1):S49–58. [PubMed: 17563290]
20. Higa DH, Marks G, Crepaz N, et al. Interventions to improve retention in HIV primary care: a systematic review of U.S. studies. Curr HIV/AIDS Rep. 2012;9(4):313–25. [PubMed: 22996171]
21. Gardner LI, Metsch LR, Anderson-Mahoney P, et al. Efficacy of a brief case management intervention to link recently diagnosed HIV-infected persons to care. AIDS. 2005;19(4):423–31. [PubMed: 15750396]
22. Saleebey D The strengths perspective in social work practice. 2nd ed. New York: Longman; 1997 p. 259.
23. Rapp CA, Chamberlain R. Case management services for the chronically mentally ill. Soc Work. 1985;30(5):417–22. [PubMed: 10273981]
24. Zimmerman MA. Psychological empowerment: issues and illustrations. Am J Community Psychol. 1995;23(5):581–99. [PubMed: 8851341]
25. Bandura A Social foundations of thought and action : a social cognitive theory. Englewood Cliffs: Prentice-Hall; 1986 p. 617.
26. Kiriazova T, Postnov O, Bingham T, et al. Patient and provider perspectives inform an intervention to improve linkage to care for HIV patients in Ukraine. BMC Health Serv Res. 2018;18(1):58. [PubMed: 29378581]
27. Neduzhko O, Postnov O, Bingham T, et al. Feasibility and acceptability of the Modified Antiretroviral Treatment Access Study (MARTAS) Intervention Based on a Pilot Study in Ukraine. J Int Assoc Provid AIDS Care. 2019;18:2325958218823257. [PubMed: 30672381]
28. Forsyth A, Yakovchenko V. Secretary Sebelius approves indicators for monitoring HHS-funded HIV services. 2012 https://www.hiv.gov/blog/secretary-sebelius-approves-indicators-for-monitoring-hhs-funded-hiv-services. Accessed 15 Jan 2019.
29. Eaton WW, Smith C, Ybarra M, et al. The use of psychological testing for treatment planning and outcomes assessment: Instruments for adults In: Maruish ME, editor. Center for Epidemiologic Studies Depression Scale: review and revision (CESD and CESD-R). Mahwah: Lawrence Erlbaum Associates Publishers; 2004 p. 363–377.
30. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977;1(3):385–401.
31. Weissman MM, Sholomskas D, Pottenger M, et al. Assessing depressive symptoms in five psychiatric populations: a validation study. Am J Epidemiol. 1977;106(3):203–14. [PubMed: 900119]
32. Babor T, Higgins-Biddle J, Saunders J, Monteiro M. AUDIT: the alcohol use disorders identification test: guidelines for use in primary health care. 2nd ed. Geneva: World Health Organization; 2001.
33. Justice AC, Holmes W, Gifford AL, et al. Development and validation of a self-completed HIV symptom index. J Clin Epidemiol. 2001;54(Suppl 1):S77–90. [PubMed: 11750213]
34. Kilbourne AM, Justice AC, Rollman BL, et al. Clinical importance of HIV and depressive symptoms among veterans with HIV infection. J Gen Intern Med. 2002;17(7):512–20. [PubMed: 12133141]
35. DHS Model Questionnaire—Phase 7 (English, French). 2015 https://dhsprogram.com/publications/publication-dhsq7-dhs-questionnaires-and-manuals.cfm. Accessed 14 Dec 2018.
36. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. 2007 https://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf?ua=1. Accessed 19 Sept 2018.

37. Gardner LI, Marks G, Craw J, et al. Demographic, psychological, and behavioral modifiers of the Antiretroviral Treatment Access Study (ARTAS) intervention. AIDS Patient Care STDS. 2009;23(9):735–42. [PubMed: 19645619]

38. Udeagu CC, Webster TR, Bocour A, et al. Lost or just not following up: public health effort to re-engage HIV-infected persons lost to follow-up into HIV medical care. AIDS. 2013;27(14):2271–9. [PubMed: 23669157]

39. Bove JM, Golden MR, Dhanireddy S, et al. Outcomes of a clinic-based surveillance-informed intervention to relink patients to HIV care. J Acquir Immune Defic Syndr. 2015;70(3):262–8. [PubMed: 26068720]

40. Turner CF, Ku L, Rogers SM, et al. Adolescent sexual behavior, drug use, and violence: increased reporting with computer survey technology. Science. 1998;280(5365):867–73. [PubMed: 9572724]

41. Des Jarlais DC, Paone D, Milliken J, et al. Audio-computer interviewing to measure risk behaviour for HIV among injecting drug users: a quasi-randomised trial. Lancet. 1999;353(9165):1657–61. [PubMed: 10335785]

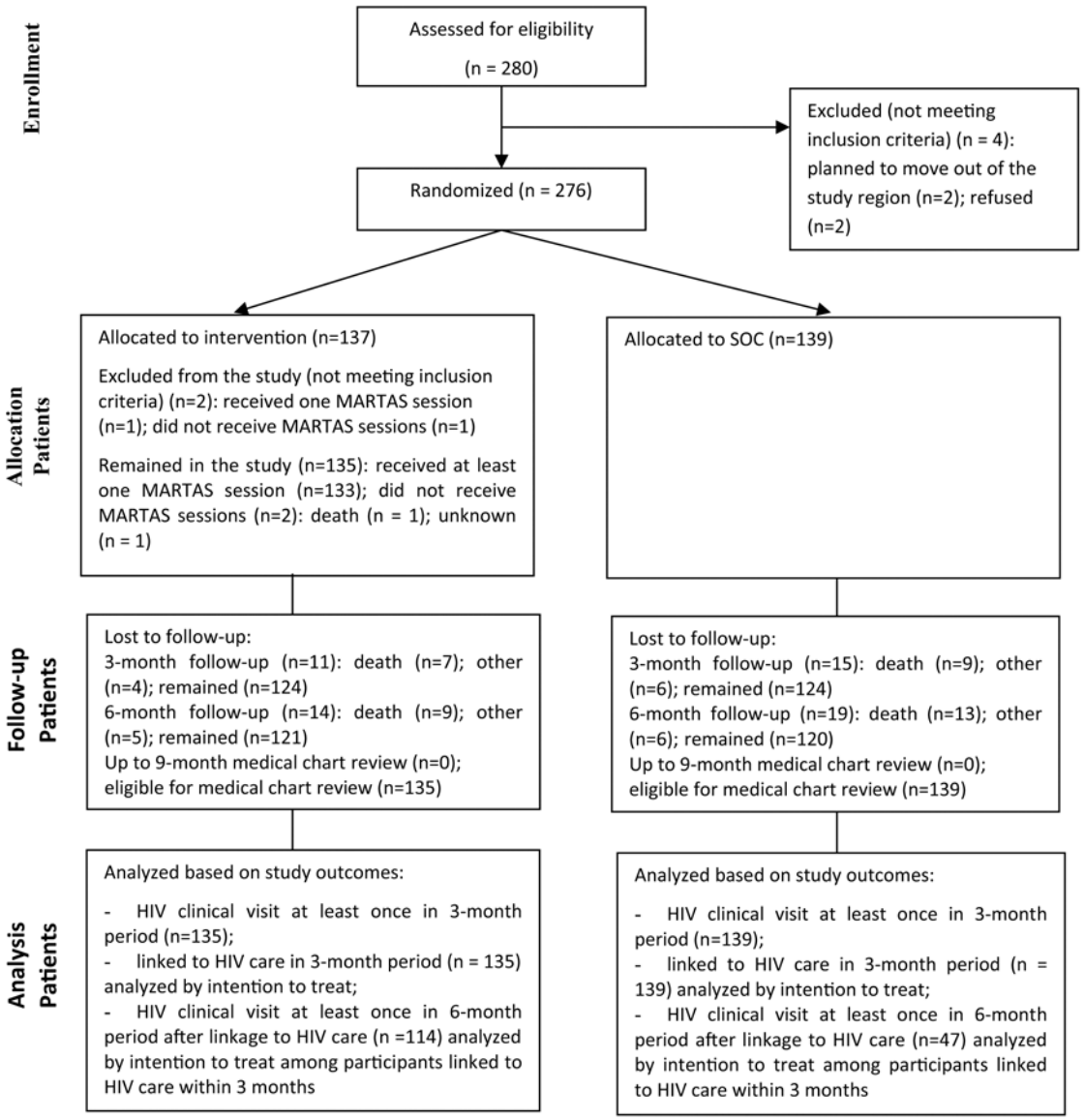

Fig. 1.
Participant flow

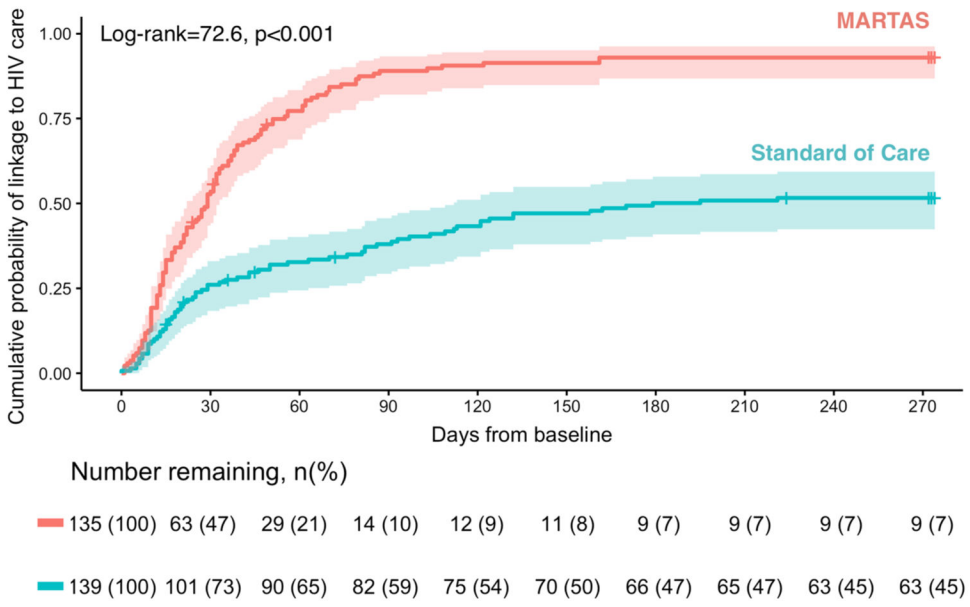

Fig. 2.

Cumulative probability of linkage to HIV care: Kaplan–Meier curves by study group for all participants (N = 274)

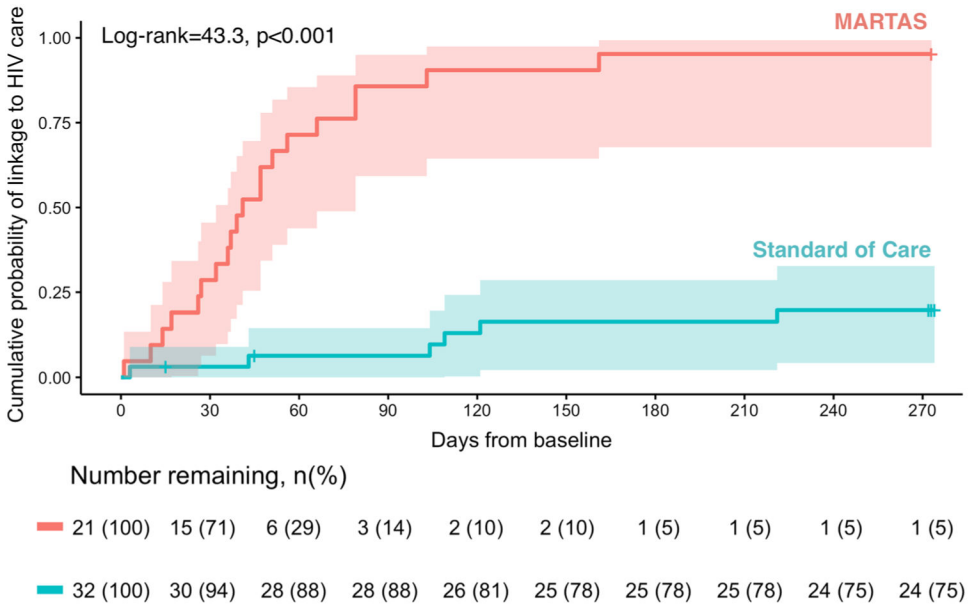

Fig. 3.

Cumulative probability of linkage to HIV care: Kaplan–Meier curves by study group for those with reported drug use within the past month excluding opioid substitution treatment or cannabis (N = 53)

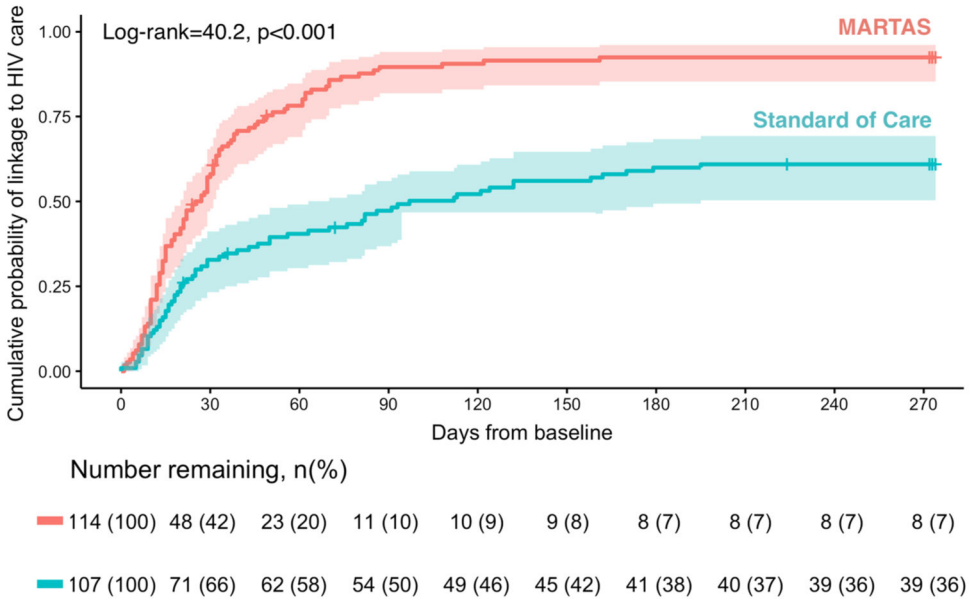

Fig. 4.

Cumulative probability of linkage to HIV care: Kaplan–Meier curves by study group for those with no reported drug use within the past month (N = 221)

Table 1

Study intervention characteristics and study modifications

Characteristic	ARTAS	MARTAS	National priorities addressed
Target population	Adults within 6–12 months of receiving an HIV-positive diagnosis	Adult HIV-positive patients from drug dependence, STI, and ID clinics who have not previously been linked to HIV care	Better access to key populations; filling of priority gaps in enrollment from drug dependence, STI, and ID clinics; accounting for epidemiological trends (concentrated stage of HIV epidemic); provider-initiated HIV testing and counselling (PITC) approach implementation in Ukraine focusing on patients with IDs, STIs and addiction
Possible implementing agencies	Health departments, AIDS service providers, HIV testing sites, Ryan White case management programs, drug treatment programs, and community-based organizations	HIV testing sites within addiction, STI, and ID clinics	Public involvement
Intervention site	Starting at testing site and moving to HIV care site	Starting at addiction, STI, and ID clinics and moving to HIV care site and community-based settings (if needed)	A high proportion of key populations are seen; HIV PITC has been implemented, so more patients are tested
Structure of program	Up to five sessions over a 3-month period or until the client links to medical care—whichever comes first	6 LC sessions (3 in person, 3 by phone), text messaging over 3 months or until the patient links to medical care with explicit engagement and retention goal	Limited local resources addressed
Content of program	Individual counseling to motivate HIV care engagement, identify barriers to care and strengths to overcome barriers	ARTAS content plus reinforcement of recovery, addressing depression, stigma, fear of HIV status disclosure, and addiction/ID/STI treatment	Addressing the highly prevalent HIV co-morbidities (ID, addiction, STIs)
Case manager/linkage coordinator role	Based at HIV clinic, trained community member, not necessarily HIV-infected peer. Delivers all intervention sessions	Based at drug dependence, STI, and ID clinics; trained nurse. Delivers all intervention sessions	Sustainable model using existing infrastructure
Addressing retention in care	Possible link to a long-term/Ryan White case manager and/or another service delivery system to address longer-term barriers to remaining in care, i.e., those beyond linkage to medical care such as substance use treatment, or mental health services	Link to an HIV physician and community manager to address (if needed) long- term barriers to remaining in care (i.e., depression, substance use treatment, ID treatment, STIs treatment)	Guaranteed continuum of care

AIDS Behav. Author manuscript; available in PMC 2020 November 01.

Table 2

Baseline sociodemographic and behavioral characteristics of participants

Characteristics	MARTAS (n = 135) n (%)	SOC (n = 139) n (%)	Total (n = 274) n (%)	Test statistic, *p*-value
Site				$\chi^2 = 0.019$, $p = 0.99$
STI clinics	64 (47.4)	65 (46.8)	129 (47.1)	
Drug dependence clinics	35 (25.9)	37 (26.6)	72 (26.3)	
ID clinics	36 (26.7)	37 (26.6)	73 (26.6)	
Age in years (min = 18, max = 66), median (IQR)	36.0 (14.0)	37.0 (13.0)	36.0 (14.0)	Mann–Whitney U = 9745.5, $p = 0.58$
Sex				
Male	85 (63.0)	89 (64.0)	174 (63.5)	$\chi^2 = 0.003$, $p = 0.95$
Female	50 (37.0)	50 (36.0)	100 (36.5)	
Relationship status				$\chi^2 = 0.068$, $p = 0.80$
Married/regular partner	74 (54.8)	73 (52.5)	147 (53.6)	
No regular partner (single, widowed, divorced, separated)	61 (45.2)	66 (47.5)	127 (46.4)	
Education				$\chi^2 = 3.290$, $p = 0.19$
Incomplete high school	33 (24.4)	25 (18.0)	58 (21.2)	
High school/vocational	73 (54.1)	90 (64.7)	163 (59.5)	
Higher (bachelor or higher)	29 (21.5)	24 (17.3)	53 (19.3)	
Employment				$\chi^2 = 0.655$, $p = 0.42$
Full-time or part-time	99 (73.3)	108 (78.3)	207 (75.8)	
No employment (unemployed, disable, retired, students, housewife, maternity leave)	36 (26.7)	30 (21.7)	66 (24.2)	
Refused to answer[a]	0	1	1	
Average monthly income ≤ 2000 UAH (≤ $80 USD)	53 (39.3)	73 (53.3)	126 (46.3)	$\chi^2 = 5.708$, $p = 0.06$
2001–4000 UAH ($80.04–160 USD)	50 (37.0)	42 (30.7)	92 (33.8)	
≥ 4001 UAH (≥ $160.04 USD)	32 (23.7)	22 (16.0)	54 (19.9)	
Refused to answer[a]	0	2	2	
Living conditions				Fisher's Exact Test, $p = 0.06$
Own apartment/house	77 (57.0)	70 (50.4)	147 (53.6)	
Renting	16 (11.9)	16 (11.5)	32 (11.7)	
Apartment/house of the partner, friends or relatives (no rent)	34 (25.2)	51 (36.7)	85 (31.0)	

Characteristics	MARTAS (n = 135) n (%)	SOC (n = 139) n (%)	Total (n = 274) n (%)	Test statistic, *p*-value
Other	8 (5.9)	2 (1.4)	10 (3.6)	
History of incarceration				$\chi^2 = 0.021$, $p = 0.89$
Yes	32 (23.7)	35 (25.2)	67 (24.5)	
No	103 (76.3)	104 (74.8)	207 (75.5)	
Drug use during last 30 days excluding cannabis and OST (injecting or/and non-injecting)				$\chi^2 = 1.992$, $p = 0.16$
Yes	21 (15.6)	32 (23.0)	53 (19.3)	
No	114 (84.4)	107 (77.0)	221 (80.7)	
AUDIT Score				$\chi^2 = 4.148$, $p = 0.25$
No or low risk of alcohol-related problems (0–7)	81 (60.4)	79 (56.9)	160 (58.6)	
Medium level of alcohol problems (8–15)	30 (22.4)	23 (16.5)	53 (19.4)	
High level of alcohol problems (16–19)	6 (4.5)	9 (6.5)	15 (5.5)	
Alcohol dependence (20+)	17 (12.7)	28 (20.1)	45 (16.5)	
Refused to answer[a]	1	0	1	
Smoking				$\chi^2 = 3.439$, $p = 0.18$
Regular smoker (≥ 1 cigarette per day)	91 (67.4)	102 (73.4)	193 (70.4)	
Occasional smoker	19 (14.1)	10 (7.2)	29 (10.6)	
Ex/ever smoker	25 (18.5)	27 (19.4)	52 (19.0)	
Depression CES-D				$\chi^2 = 0.008$, $p = 0.93$
Depression symptoms (≥ 16 points)	76 (56.3)	80 (57.6)	156 (56.9)	
No clinical significance	59 (43.7)	59 (42.4)	118 (43.1)	
HIV Symptoms Index (frequency of symptoms), (min = 0, max = 17), median (IQR)	8.0 (6.0)	7.0 (6.0)	8.0 (6.0)	Mann–Whitney U = 9228.5, p = 0.81
HIV bothersome symptoms index (frequency of symptoms), (min = 0, max = 17), median (IQR)	2.0 (5.0)	2.0 (5.0)	2.0 (5.0)	Mann–Whitney U = 9201, $p = 0.78$
HIV status disclosure				$\chi^2 = 0.002$, $p = 0.97$
No disclosure	46 (34.1)	46 (33.1)	92 (33.6)	
Disclosed to ≥ 1 persons	89 (65.9)	93 (66.9)	182 (66.4)	
HIV knowledge				$\chi^2 = 1.270$, $p = 0.26$
Correct answers to all 10 questions	15 (11.1)	23 (16.5)	38 (13.9)	
Gaps in knowledge	120 (88.9)	116 (83.5)	236 (86.1)	
Time since HIV positive testing to study entry				Fisher's Exact Test, $p = 0.45$
0–6 months	132 (97.8)	133 (95.7)	265 (96.7)	

AIDS Behav. Author manuscript; available in PMC 2020 November 01.

Characteristics	MARTAS (n = 135) n (%)	SOC (n = 139) n (%)	Total (n = 274) n (%)	Test statistic, *p*-value
7–12 months	2 (1.5)	2 (1.4)	4 (1.5)	
≥ 13 months	1 (0.7)	4 (2.9)	5 (1.8)	

[a] Category was excluded from hypothesis testing

Table 3

Factors associated with successful linkage to HIV care at 3 months among participants enrolled in the MARTAS randomized controlled trial in Ukraine, 2015–2018

Characteristics	Linked within 3 months (n = 161) n (%)	Not linked or linked after 3 months (n = 113) n (%)	Crude relative risk (95% CI), *p*-value	Adjusted relative risk (95% CI), *p*-value
Intervention arm				
MARTAS	114 (84.4)	21 (15.6)	2.50 (1.96–3.19), $p < 0.001$	2.45 (1.72–3.47), $p < 0.001$
SOC	47 (33.8)	92 (66.2)	Ref	Ref
Sex				
Male	94 (54.0)	80 (46.0)	0.81 (0.66–0.98), $p = 0.030$	0.88 (0.64–1.23), $p = 0.46$
Female	67 (67.0)	33 (33.0)	Ref	Ref
Education				
Incomplete high school	34 (58.6)	24 (41.4)	0.84 (0.64–1.11), $p = 0.22$	0.86 (0.53–1.41), $p = 0.56$
High school/vocational	90 (55.2)	73 (44.8)	0.79 (0.63–0.99), $p = 0.041$	0.90 (0.60–1.33), $p = 0.58$
Higher (bachelor or higher)	37 (69.8)	16 (30.2)	Ref	Ref
Living conditions				
Own apartment/house	88 (59.9)	59 (40.1)	0.75 (0.53–1.05), $p = 0.09$	1.02 (0.49–2.13), $p = 0.96$
Renting	20 (62.5)	12 (37.5)	0.78 (0.52–1.18), $p = 0.24$	1.06 (0.46–2.43), $p = 0.89$
Apartment/house of the partner, friends or relatives (no rent)	45 (52.9)	40 (47.1)	0.66 (0.46–0.96), $p = 0.028$	1.07 (0.49–2.32), $p = 0.87$
Other	8 (80.0)	2 (20.0)	Ref	Ref
History of incarceration				
Yes	30 (44.8)	37 (55.2)	0.71 (0.53–0.94), $p = 0.018$	0.89 (0.56–1.41), $p = 0.63$
No	131 (63.3)	76 (36.7)	Ref	Ref
Drug use during last 30 days excluding cannabis and OST (injecting or/and non-injecting)				
Yes	19 (35.8)	34 (64.2)	0.56 (0.38–0.81), $p = 0.002$	0.66 (0.39–1.13), $p = 0.13$
No	142 (64.3)	79 (35.7)	Ref	Ref
Smoking				
Regular smoker (≥ 1 cigarette per day)	105 (54.4)	88 (45.6)	0.81 (0.64–1.02), $p = 0.07$	0.94 (0.62–1.42), $p = 0.76$
Occasional smoker	21 (72.4)	8 (27.6)	1.08 (0.80–1.44), $p = 0.63$	0.92 (0.52–1.61), $p = 0.77$
Ex/ever smoker	35 (67.3)	17 (32.7)	Ref	Ref

Characteristics	Linked within 3 months (n = 161) n (%)	Not linked or linked after 3 months (n = 113) n (%)	Crude relative risk (95% CI), *p*-value	Adjusted relative risk (95% CI), *p*-value
Depression CES-D				
Depression symptoms (≥ 16 points)	97 (62.2)	59 (37.8)	1.15 (0.93–1.41), $p = 0.19$	1.17 (0.85–1.62), $p = 0.34$
No clinical significance	64 (54.2)	54 (45.8)	Ref	Ref

Model adjusted for all covariates listed